

FINAL REPORT

RESEARCH CONTRACT NO. NASA NCC 9-20

*FINAL
IN-51-012
OCIT
125936*

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CONTRACT TITLE: Study of Hind Limb Tissue Gas Phase Formation in Response to Suspended Adynamia and hypokinesia

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INTRODUCTION:

The purpose of this study was to investigate the hypothesis that reduced joint/muscle activity (hypo kinesia) as well as reduced or null loading of limbs (adynamia) in gravity would result in reduced decompression-induced gas phase and symptoms of decompression sickness (DCS). Finding a correlation between the two phenomena would correspond to the proposed reduction in tissue gas phase formation in astronauts undergoing decompression during extravehicular activity (EVA) in microgravity. The observation may further explain the reported low incidence of DCS in space.

BACKGROUND:

Operationally important medical challenges of manned space flight include microgravity-induced cardiovascular deconditioning, total body calcium loss, and the risk

of decompression sickness (DCS) during extravehicular activity (EVA). Altitude DCS deserves particular attention because it is a preventable complication, but one that can have serious consequences if left unattended (53). Evaluation of the interaction between microgravity exposure and decompression illness is appropriate in view of plans for extended duration missions and an overall increase in the number of EVAs required for construction of the space station. It is intended that such investigation will lead to a better understanding of the interplay between DCS and the human cardiovascular system in a microgravity environment.

Decompression sickness results from the formation and growth of gas bubbles within the tissues and venous blood, e.g., venous air emboli (VAE). Associated symptoms can range from mild skin itching or simple joint pain to central nervous system involvement and even cardiovascular collapse. The pathophysiology of DCS may also impact the lungs as the venous bubbles obstruct the pulmonary microcirculation (13,18) decreasing cardiac output (CO), increasing pulmonary vascular pressures and altering lung fluid balance. The preponderance of actual symptoms, however, involve limb pain that are presumably caused by extravascular bubbles.

Animal models have offered numerous insights into the mechanisms and etiologies of the symptoms of DCS. The smaller animal models usually require more extreme decompression exposures before more typical symptoms are manifested. These symptoms may also be far more severe than occurs routinely in the human clinical situation, especially where actual mortality rates are reported. The rat, for example, is a model commonly used in experimental DCS, but often requires greater extremes in decompression protocols (6,40,51). As a result, the more subtle effects of DCS are often overshadowed by the onset of a severe circulatory or pulmonary complications. Large animals such as the goat and sheep have been useful in evaluating the effects of decompression profiles in terms of limb pain (3,8,38) or respiratory complications (3), whereas the dog and swine have been used for hemodynamic assessment (7,17,58).

Flynn and Lambertsen (27) reported on a number of animal models of log-log relationship between body weight and the nitrogen dose required to produce DCS.

Of equal importance in drawing conclusions from one species or measurement to another is the type and accuracy of symptom or measurement being made. The purpose of the present study was to examine the effects of moderate decompression stress in terms of cardiovascular function and pulmonary responses in chronically, instrumented, conscious rats using a profile that was well below a threshold of significant mortality.

The adaptation of the cardiovascular system to the microgravity environment (cardiovascular deconditioning) appears to be due in part to a cephalad fluid shift and has been extensively studied in the conscious rat (45). Astronaut EVAs have brought into question the potential relationship between cardiovascular deconditioning and hypobaric DCS. Compared with careful ground-based studies conducted in hypobaric chambers, there is a lower incidence of DCS in space during the astronaut EVAs that would be predicted (52). These studies have established the predicted incidence of DCS expected, both in relation to the final altitude following a direct or staged decompression and, subsequent to washout of tissue inert gas (e.g. nitrogen) by oxygen pre-breathing prior to decompression (26). In addition, other factors such as exercise, ambulation, time at altitude and individual susceptibility have been examined (2). The interaction between hypobaric decompression and the deconditioned cardiovascular system has not been previously evaluated. The purpose of this study was to assess pulmonary and hemodynamic effects of simulated microgravity and hypobaric decompression illness in the conscious rat.

METHODOLOGY:

Principle. Two series of studies were conducted. The first was to evaluate the cardiopulmonary changes with moderate decompression in rats. The second was to study the effects of tail-suspension cardiovascular deconditioning and venous air embo-

lism in simulated microgravity in the rat. The combined procedures of chronic instrumentation, tail-suspension deconditioning and decompression were found to compromise overall evaluation. Therefore, the procedures were separated such that instrumentation and decompression were evaluated in one series and instrumentation, tail-suspension and venous air infusion (simulating both microgravity deconditioning and decompression sickness) in the second series.

Overview: All experiments and procedures were approved by the Institutional Animal Care and Use Committee at The University of Texas Medical School at Houston. Sprague-Dawley rats were used to study the cardiac function and pulmonary changes with decompression. In the first series of studies, the rats were divided into two groups, one using chronically instrumented, awake rats for cardiovascular function assessment and the second using non-instrumented rats for pulmonary measurements. The pulmonary group was subdivided into groups 2-4 (2 controls, 3 those monitored 0 min post decompression, and 4 those monitored 60 min post decompression). In the second series, six groups of rats were studied. Groups 1 and 2 were used to assess the hemodynamic effects of tail-suspension with and without venous air infusion, whereas groups 3-6 were used for biochemical analysis. Each animal served as its own control.

I. Cardiovascular Function

a) *Instrumentation:* The rats were anesthetized with halothane, intubated and ventilated under isothermic conditions. A left parasternal thoracotomy was performed and the pericardium exposed and sectioned. A 20-MHZ pulsed Doppler flow probe was then placed around the ascending aorta for cardiac output measurement. The displacement probe used to measure left ventricular wall thickening was sutured to the left ventricular wall and an 18 gauge thoracic drain was positioned until closure of the thorax.

The ultrasonic flow probe leads were tunneled to the dorsum of the neck for externalization and the surgical wounds closed. Polyvinyl catheters were placed into the abdominal aorta via the femoral artery and the jugular vein for measurement of arterial blood pressure and central venous pressure. The catheters were also tunneled to the neck dorsum. The lungs were reinflated under vacuum and the wounds were infiltrated with bupivacaine (0.5%) for post-operative analgesia. Antibiotic therapy (gentamycin 5 mg/kg IM) was initiated for a minimum of 5 days. The animals were weighed daily and inspected for signs of infection.

The single-crystal pulsed Doppler technique for measurement of changes in myocardial wall thickening fraction has previously been described in detail (34). The displacement modules operated at a pulse repetition frequency of 8 KHz and an ultrasonic frequency of 20 MHz. The pulsed Doppler system measured displacement of myocardial tissue through a sample volume with the use of a single crystal which alternately serves as transmitter and receiver. Briefly, it operates by integrating the velocity of the various myocardial layers that pass back and forth through a range-gated sample volume located within the myocardium at a fixed distance from the epicardial surface where the crystal is attached to the myocardial wall. Thickening fraction is defined as the maximum excursion recorded during systole, divided by the sample volume depth. The range was set a 2-3 mm depth near the endocardium.

The pulsed Doppler system for measurement of cardiac output in small animals has also been described in detail (35). Briefly, a linear relationship between true volume flow and Doppler frequency shift has previously been demonstrated in a variety of blood vessels with diameters ranging from 1 to 11 mm. At a pulsed repetition frequency (PRF) of 125 KHz, the Doppler system resolves frequency shifts of up to 62.5 KHz (PRF/R) at a maximum range (R) from 0.6 to 6 mm and a spatial range of 0.3 mm. True blood flow was calculated from the maximum Doppler frequency shift using the standard relationship described by Ishida et al. (37). The Doppler flow probes were manufactured according to previously described techniques (34,35).

b) *Hemodynamic Measurements:* All hemodynamic variables [e.g. heart rate (HR), mean arterial (MAP) and central venous pressure (CVP), left ventricular wall thickening (WT), and cardiac output (CO)] were processed with the multichannel pulsed Doppler flow/dimension system and were continuously displayed on a Gould physiograph. The wall thickening fraction (TF%) was calculated as $100 \times SE/R$ (SE, the systolic excursion and R, the range-gate depth). Systemic vascular resistance (SVR) was calculated as MAP/CO .

c) *Pulmonary Edema Measurement:* The amount of blood-free extravascular fluid (edema) formation was measured using a modified method of Pearce (48) to account for the residual blood volume in the organ. The extravascular lung water (EVLW) was expressed as the extravascular fluid to dry weight ratio.

d) *Lung Compliance:* For quasi-static lung compliance measurement, the lungs were isolated, degassed under vacuum (56), placed in a heated humidified chamber and connected via a tracheal catheter to an infusion/withdrawal pump and an airway pressure transducer. The lungs were inflated to 30 cm H₂O at a rate of 20 ml/min, equilibrated for 15 min while maintaining 30 cm H₂O pressure. Inflation/deflation pressure-volume curves were then collected. The compliance measurements were taken from the deflation limb of the curve between 30% and 70% of total lung capacity.

e) *Bronchoalveolar Lavage (BAL):* The trachea was cannulated and the airways were lavaged with 10 ml cold normal saline (5°C). This procedure was repeated 6 times for a total lavage volume of 60 ml. The BAL samples were pooled. Total BAL protein was assayed using the Lowry method with modification for the presence of lipid from the 60 ml pooled lavage (39). BAL hemoglobin levels were measured using a modified benzidine assay.

f) *Cell Counts:* Total white cell counts were performed on BAL, pulmonary and arterial blood and pleural fluid using a Neubauer hemocytometer with EDTA stabilization. Differential cell counts were performed with microscopic survey using Wright-Geimsa stain.

Data Analysis: Data were analyzed using ANOVA with Dunnett's correction for the individual comparisons in the biochemistry studies. The cardiovascular data were analyzed using a 2-way ANOVA. Individual comparisons were analyzed using Student's t-test with Bonferroni correction. Significance was considered at $p < 0.05$.

Procedure (Decompression Studies): The conscious rats were placed in a rodent restraint apparatus and acclimated to the chamber environment before collection of baseline data. The chamber was then compressed to 616 kPa at 34 kPa/min for a bottom time of 120 min, then decompressed to sea level at 38 kPa/min. Hemodynamic monitoring continued throughout the compression/decompression procedure and for 120 min after. The chamber environment was maintained at room temperature ($\pm 4^{\circ}\text{C}$) during both compression and decompression with a constant fresh air flow.

Pulmonary measurements (Groups 2-4, $n = 60$)

Group 2 rats (440 ± 59 g) consisted of non-decompressed controls, group 3 rats (421 ± 57 g) were decompressed and measurements taken immediately after the decompression (0 min post decompression), and group 4 rats (406 ± 27 g) were decompressed and measurements taken 60 min post decompression. At 0 to 60 min post decompression, the rats were anesthetized (pentobarbital sodium, 50 i.p.) and an arterial blood sample was collected anaerobically from the abdominal aorta for blood gas, plasma protein, and white blood cell analysis. Pulmonary artery blood samples were collected by direct puncture of the pulmonary artery following thoracotomy. The animals were then exsanguinated, pleural fluid collected, and the lungs removed for measurement of compliance, bronchoalveolar lavage (BAL) collection, and extravascular lung

water (pulmonary edema) measurement. Not all measurements were obtainable from each rat. The number of rats/measurement are listed in the tables.

Procedure (Tail-Suspension (TS) VAE Studies): Group 1, (n=8) designated VAE, was exposed to 3 hrs of venous air infusion. We elected to use VAE given as a continuous infusion to simulate the prolonged bubbling that is reported with hypobaric decompression exposures used to simulate an astronaut (EVA). In these cases, VAE are detected with Doppler ultrasound probes for periods lasting several hours during the period of decompression. Injecting venous gas very slowly in the rat simulated that particular feature of decompression effects. Although this technique is well established for a number of species (38), little data is available for the rat. After hemodynamic parameters stabilized, rats received the venous air infusions into the central venous catheter at a rate of $0.015 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 180 min. Cardiovascular data were recorded at 15, 30, 45, 60, 120 and 180 minutes during venous air infusion and at 15, 30, 45 and 120 minutes and 24 hrs post infusion.

Group 2 (n=8) designated TS-VAE, experienced cardiovascular deconditioning by tail-suspension (TS) with a 30° head-down tilt. The tail suspension model has previously been described in detail (44) and is widely used by investigators to simulate the fluid shifts commonly observed upon exposure to microgravity. Briefly, rats were fitted with a flexible foam-tape cast applied to the proximal half of the tail. The cast was attached to a swivel and the rats were suspended in a 30° head-down tilt. This apparatus allowed the rats to rotate in a 360° arc using their forelimbs and permitted free access to food and water in a light/dark cycled environment. Following 96 hrs tail-suspension and while maintained in the suspended position, the animals were infused with venous air for 3 hrs as described above.

Pulmonary Measurements (Groups 3-6)

Group 3 consisted of normoactive controls, Group 4, tail-suspension only, Group 5, VAE only and Group 6, tail-suspension-VAE. The rats in groups 5 and 6 received

venous air infusions, as described above. Immediately post infusion, the animals were anesthetized with pentobarbital sodium (50 mg IP). An arterial blood sample was collected anaerobically for blood gas and plasma protein analysis. The animals were euthanized by exsanguination and the lungs were removed for the following measurements.

RESULTS

I. Decompression Studies

The decompression profile used in this study was selected to produce saturation conditions with moderate bubbling and symptoms. Venous bubbles were visually observed in 90% of the rats examined immediately following decompression (Group 3), while only 3% (2/60) demonstrated gross symptoms of DCI (hindlimb paralysis, severe respiratory complications, etc.). Doppler bubble detection in the instrumented rats (Group 4) was less conclusive, demonstrating bubbles in 37% (7/19) in rats in which the probe functioned properly. The insensitivity of the Doppler data may be attributable to the placement of the probe on the right ventricular wall versus the more common precordial site where effective sampling of all venous blood is more assured. Quantitation of the bubbles in terms of size or count was not undertaken in these studies.

a. *Blood Gas Measurements:* (Table 1) Arterial PO_2 values were decreased in Group 3 rats (nonsignificant) and elevated in Group 4 (significant). $PaCO_2$ values were significantly increased (44.9 ± 2.4 mmHg to 51 ± 1.8 mmHg) in Group 3 ($p < 0.05$) and were unchanged in Group 4. Increased respiratory frequency with decreased tidal volumes were observed visually in 68% of the rats 0 min. post decompression. These rats had $PaCO_2$ values significantly higher (53 ± 8 mmHg) than those without respiratory symptoms (47 ± 11 mmHg) or from the control Group (44.9 ± 2.4 mmHg).

b. *Pulmonary Measurements:* (Table 2) BAL hemoglobin values were increased in Groups 3 and 4 by 7.5 and ($p < 0.05$) 17 fold, respectively. BAL total protein was increased in Groups 3 and 4 (36% and 77%; Group 4, $p < 0.05$). The BAL protein/plasma protein ratio was also significantly increased in Group 4 compared to controls. Plasma

protein levels were unchanged. Pleural protein and Hb values were unchanged. Lung compliance was decreased by 10% in Group 3 and 16% in Group 4 (non significant).

c. *Cell Counts:* Pulmonary blood white cell counts (WBC) were increased in Group 4 (Figure 1, Bottom). The percentage of arterial and pulmonary WBC that were neutrophils was slightly elevated (nonsignificant) in both groups (Figure 1, Top). Pleural fluid WBC was decreased in Group 3, a dilutional effect, while the percentage of neutrophils was increased in Group 4 ($p < 0.05$). BAL WBC increased significantly in both Groups 3 and 4 (121% and 212%, respectively), as did the percentage of neutrophils in Group 4 (Figure 1, Top).

d. *Pulmonary Edema Measurement:* Extravascular lung water (wet/dry weight ratio) was significantly elevated in Group 4, 60 min. post decompression (Table 2). Cut lung surfaces often revealed perivascular cuffs of edema fluid, especially around larger vessels. Excess airway fluid was not observed.

e. *Cardiovascular Measurements:* (Figure 2) Mean arterial blood pressure was significantly elevated at the end of the compression period and unchanged post decompression. Heart rate was unchanged throughout the compression/decompression protocol. Cardiac output (Figure 3) was unchanged throughout the compression period, decreased upon return to sea level pressure (21%, $p < 0.05$) and remained decreased for 60 min. post decompression (21%, $p < 0.05$). Comparable changes occurred with stroke volume, with a greater degree of recovery, however (18% from baseline) 120 min. post decompression. Systemic vascular resistance (Figure 2) was unchanged during the period of compression, increased significantly 0 min. and 60 min. post decompression (65% and 70%) and remained elevated for 120 min. (34%).

Left ventricular wall thickening fraction (TF) was unchanged for all groups, while right ventricular TF (Figure 3) was decreased significantly 0 min. and 60 min. post decompression.

II. Tail-Suspension Studies

Cardiovascular Measurements: In the TS-VAE group, SVR increased significantly by 28% from the onset of tail-suspension and remained elevated throughout the venous air infusion (Figure 4). In the VAE group, SVR increased significantly by 23% above baseline within 60 min of venous air infusion and remained elevated for 5 hrs. SVR in the VAE group returned to baseline within 6 hrs. CVP remained unchanged in both groups.

Cardiac output in the VAE group decreased by 26% by the end of the 180 min venous air infusion (Figure 4). This was significantly greater than the TS-VAE group whose CO decreased by 9%. In the TS-VAE group however, tail suspension alone caused a 11% decrease (non-significant) in CO prior to the venous air infusion. Decreases in CO from baseline were significant at 1, 2 and 3 hours of venous air infusion for both TS-VAE and VAE groups, versus control. CO returned to baseline within 3 hrs. after venous air infusion. Arterial blood pressure was not significantly altered by either the tail-suspension or VAE. WT remained unchanged in response to tail-suspension or venous air infusion..

TS-VAE and VAE rats showed a similar response in heart rate to venous air infusion. HR decreased significantly by the first hour of air infusion and remained decreased until the end of the infusion. The differences between the two groups were not significant. In both groups, HR returned to baseline within 6 hrs. (Figure 5).

Pulmonary Measurements: In the VAE group, lung wet to dry ratio was increased significantly as compared to the three other groups. TS-VAE rats also showed a significant increase in lung wet to dry ratio as compared to the control group. Tail suspension alone did not cause a significant increase in extravascular lung water. Arterial blood gas values, pH, PaCO₂ and PaO₂ were not different from control value in any experimental group, although the decrease in PaO₂ and the increase in PaCO₂ seen in the VAE and TS-VAE groups were consistent with the pathologic pulmonary changes reported with DCI. Pulmonary compliance was unchanged in all experimental groups (Table 3).

Total arterial white blood cell counts (WBC) were unchanged in all experimental groups (Table 4, top). Pulmonary arterial blood white cell counts were significantly increased however, in the VAE group versus controls, but neither the TS or the TS-VAE groups showed significant differences from the control group. Pleural fluid white blood cell count was decreased in the VAE group versus the controls. This appeared to be a dilutional effect due to an increase in pleural fluid volume. BAL WBC counts were unchanged. Arterial blood neutrophil counts in both the TS-VAE and the VAE groups were significantly increased over control. Pulmonary and systemic arterial neutrophil counts were significantly increased in both the VAE and the TS-VAE groups versus the control group (Table 4). Pleural fluid neutrophil counts were increased significantly in all experimental groups versus the control.

Pleural fluid protein concentration was increased in the VAE group versus the controls, but there was no significant change in either the TS or the TS-VAE groups.

Plasma protein levels were unchanged (Table 4, bottom). BAL protein was unchanged in both TS-VAE and in VAE rats (Table 4).

DISCUSSION

I. Decompression Studies

The data reported in this study further demonstrate the utility of the rat model in the evaluation of cardiovascular and pulmonary responses to moderate decompression stress. Changes in cardiovascular parameters are consistent with those reported in other species such as the dog or the pig (7,17,58). MAP values are commonly increased (often nonsignificant) with moderate decompression exposures in the larger species. We observed an increase in MAP during compression only with no changes post decompression. Decreases in HR have been reported during compression, while increases lasting up to several hours post decompression or no change at all have also been reported (7,58). In our study, the increase in HR observed 60 min. post decompression was not significant. Changes in HR may be attributable to sympathetic stimulation or changes in PaCO₂ while concomitant increases in system vascular resistance may also be a result of direct sympathetic stimulation or a result of catecholamine release (13,19).

Previous studies have reported a decrease in CO following an increase in pulmonary vascular resistance (46). Others have suggested that decompression-induced decreases in CO may be due to changes in venous return, increased load on the right ventricle as a result of the obstructed pulmonary circulation or to increased afterload on the left ventricle due to the elevated system vascular resistance (17,46,58).

Our data suggest that a decrease in venous return may be responsible for the decrease in CO recorded after decompression. Evidence supporting this concept includes:

- 1) The decrease in right thickening fraction (TF) related to either a decrease in an intrinsic cardiac inotropism or a decrease in venous return. Both mechanisms have been previously described. Right ventricular failure may occur because of myocardial ischemia resulting from a decrease in coronary blood flow due to a decrease in coronary perfusion pressure, (e.g., decrease in aortic diastolic pressure associated with elevated right ventricular end-diastolic pressures) (36) or a failure of the right ventricle to compensate for the increase in pulmonary vascular resistance due to the presence of bubbles following decompression. However, it is unlikely that a decompression-induced right ventricular failure was involved in the decrease in TF. Thus, the TF decreased only in the right ventricle after decompression. Furthermore, the changes cited above are reported with more severe cases of DCS or with air embolization where right ventricular pressures are greatly increased.
- 2) In the absence of cardiac failure, a decrease in venous return is associated with a decrease in preload of the left ventricle.
- 3) It is established that in the absence of preload changes, an increase in afterload (e.g., systemic vasoconstriction) is associated with a compensatory increase in cardiac contractility to maintain cardiac output. This is reflected as an increase in left TF (Starling's Law).

In our experimental conditions, left TF remained unchanged despite an increase in systemic vascular resistance and decrease in CO. Therefore the lack of expected left TF increase also represents an argument in favor of a decrease in venous return occurring after decompression. Any additional effects of venous bubbles or mediator-induced changes in venous resistance and/or capacitance may also have contributed to a decrease in venous return.

Pulmonary effects of decompression-induced or exogenously introduced venous bubbles include their interactions with cellular components of the blood. Such interactions include platelet and neutrophil activation and the associated release of bioactive mediators including; serotonin, histamine, kinins, prostaglandins, lymphokines, thromboxanes and leukotrienes (16,24,50,59). These agents can alter microvascular membrane and epithelial permeability and vascular tone, leading to pulmonary edema formation (16). This was evident in the present study by an increase in EVLW as well as increases in WBC's in BAL and pulmonary blood as well as neutrophil percentages in pleural and BAL fluid. Ohkuda et al. (47) and others have demonstrated pulmonary edema with venous air infusion suggesting a reversible change in permeability of the microvascular membrane. Catron et al. (18) and Peterson et al. (49) reported pulmonary edema after DCS or venous air infusion without an increase in left ventricular end-diastolic pressures. These observations are consistent with the reported data and suggest that even with moderate decompression, some change in lung fluid balance is possible. Similar changes have been reported with widely variable pressure exposures in animals and man (7,16,18,32,33). The significant increases in lysophosphatidylcholine are consistent with other studies suggesting its role in altering lung fluid balance, espe-

cially regarding changes in BAL (14). Venous air embolism in dogs has been shown to cause pulmonary endothelial disruption, platelet and leukocyte adherence to bubble surfaces and increases in leukocyte counts and degranulation (1,43). Similar findings have been reported in mesenteric vessels after decompression in rats (50) and in pulmonary vessels in mice (5). The results of this study demonstrate cardiovascular function and pulmonary changes with moderate DCS in the rat. They further demonstrate that the effects of circulating bubbles can be measured physiologically even in a small animal model at moderate decompression exposures and parallel many of the reported changes that are seen with larger animals and man.

II. Tail-Suspension Studies

Previous reports describing cardiopulmonary responses to significant decompression illness included hypotension, pulmonary hypertension, pulmonary edema, decreased lung compliance, hemoconcentration and hypoxemia (7,15,18,21,30). In similar conditions, Bove et al. observed increased systemic vascular resistance, tachycardia, increased central venous pressure and decreased cardiac output (7). Cardiovascular symptom expression and severity depend primarily on the extent of the decompression injury and hence the degree of venous bubble formation. In our experimental design, the use of a venous air dose standardized by weight, insured that the venous gas insult was uniform throughout the study population. Our findings demonstrate an attenuation in the response to both pulmonary edema formation and the decrease in cardiac output with simulated weightlessness and venous embolization (TS-VAE group).

Several mechanisms may be involved in the response of the deconditioned cardiopulmonary system to venous air embolization. The changes in cardiac output may be due to either fluid shifts or to a direct effect on myocardial function. The effects on the lungs include vascular distension, changes in volume, changes in ventilation to

perfusion matching and potential changes in diffusing capacity (55). Additional factors may include mediator-induced changes in vascular tone and endothelial permeability (54), lymphatic recruitment (57), as well as hypoxic pulmonary vasoconstriction.

In the present study, there was a slight but non-significant decrease in cardiac output with tail suspension, a finding that in magnitude is consistent with other studies (9). This change could be expected to prolong recovery from a venous gas insult, possibly by decreasing pulmonary blood flow and thereby reducing the rate of gas embolus washout. However, venous air infusion produced an acute decrease in cardiac output in all animals, whereas in the TS-VAE group, the decrease in cardiac output was significantly less than the decrease experienced by the VAE alone group. It might therefore be inferred that even though both groups demonstrated approximately the same total decrease in cardiac output, the initial decrease experienced by the TS-VAE group occurred prior to the VAE and therefore may have allowed for compensatory changes to occur.

The result of a higher cardiac output in the TS-VAE group (after first hour of air infusion) relative to the VAE group may have allowed an increase in pulmonary perfusion enabling deeper penetration of the emboli into the pulmonary vascular tree. The emboli would thus block a smaller segment of the pulmonary vasculature and therefore obstruct less of the pulmonary blood flow. This could result in a lower pulmonary artery pressure and less edema formation. A higher cardiac output might also increase the diffusion of gas from the emboli into the surrounding blood by exposing the emboli to a greater volume of blood per unit time, resulting in a more rapid rate of resolution (42). This process might also be influenced by accumulation of protein and coagulation products at the blood-bubble interface (50). Measurement of left ventricular myocardial wall thickening fraction, an indicator of myocardial contractility, demonstrated no direct effects of either tail suspension or venous air emboli on the myocardium.

We observed that the systemic vascular resistance was increased initially in the TS-VAE group, in response to tail-suspension, with no further increase during venous

air embolization. An analogous response in the pulmonary circulation, especially when venous bubbles obstruct pulmonary vessels, could result in a smaller increase in pulmonary artery pressure with venous air embolization than would be expected, leading to a decrease in pulmonary edema formation. Direct evidence for such a mechanism is unavailable.

The decrease (nonsignificant) in HR with the VAE in both groups was consistent with other reports of VAE or decompression in dogs (12,15). Possible mechanisms may include a bundle branch block if the insult was sufficient to cause myocardial ischemia (22) or a reflex-mediated response where the right heart chamber volumes are overwhelmed due to the venous gas challenges (10). Both of these mechanisms are usually reported with large VAE doses, however, that are sufficient to cause systemic hypotension.

Simulated microgravity has been shown to improve ventilation to perfusion ratio via central fluid shifts (26). This might improve tolerance to pulmonary air emboli by both maximally recruiting the pulmonary vasculature and by optimizing the lung's ability to exchange gas, thereby eliminating the gas via the alveoli. This too could result in a decrease in pulmonary edema formation, as seen in our studies.

Indirect effects of venous air bubbles include neutrophil activation and mediator release (16,54) resulting in modification of vascular permeability and tone with consequent pulmonary edema formation. Evidence of this process was observed in all animals exposed to venous air infusion. Arterial, pleural and pulmonary arterial neutrophil percentages were increased in both the TS-VAE and the VAE groups, but only the VAE group showed significant changes in systemic arterial and pleural total white blood cell count, suggesting a possible mechanism for increased mediator activation in the VAE group as compared to the TS-VAE group. The decreased BAL and pleural protein values further suggest that the permeability of the microvascular and alveolar membranes were less affected in the tail-suspension-VAE rats than the VAE alone.

Conclusions drawn from the present study are subject to certain limitations. It has been shown by other investigators that venous gas emboli will be distributed according to the gravity vector. However, Chang et al. reported that the size of the bubble, the speed of the blood flow and the size of the vessels do play a role. The authors found that under most circumstances, the emboli followed the higher branch of a bifurcation (20). While the current model mimics the greater homogeneity in blood flow seen in microgravity, one would still expect a preponderance of emboli in the "upper" lobes. Additionally, the bubbles produced by venous air embolization are larger than DCS-induced bubbles, consequently some differences in pulmonary arterial occlusion patterns and possibly in surface-area dependent processes such as cellular activation and lung fluid balance might be expected. Although the results of the present study reflect some cardiopulmonary changes, clinical symptoms of DCS involving limb pain are usually attributed to extravascular gas.

Several theories have been reported to explain the observed low incidence of hypobaric decompression illness during EVA. A decrease in the formation of micronuclei due to reduced stress on the muscles, tendons and ligaments of the joints as a consequence of reduced activity (exposure) in the microgravity environment has been described (52). Additional reasons may involve actual reporting discrepancies related to operational factors such as crew motivation, redirected attention, masking of subtle pain, misinterpreting actual symptoms or actual reluctance to report DCS (4). The results of the present study do suggest however, that more than one process may be responsible for the decreased incidence of DCS (at least in terms of cardiopulmonary effects), including an overall increase in tolerance to the combined effects of simulated microgravity and decompression.

NOTE: Much of this report was adapted directly from the published articles authored by Principal Investigator, and include verbatim passages. These references are:

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ACKNOWLEDGEMENTS

The technical assistance of Yangyan Liang and secretarial support of Caroline Buggs-Warner, for preparation of the manuscripts and reports, are graciously acknowledged.

PUBLICATIONS RESULTING FROM CONTRACT NO. NCC 9-20

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Table 1: Lung Function and Blood Gas Data

	CONTROL	POST DECOMPRESSION	
		(0 min)	(60 min)
Compliance (ml/cmH ₂ O)	1.10 ± 0.02 (4)	1.00 ± 0.05 (5)	0.92 ± 0.06 (9)
TLC (ml)	22.1 ± 0.04 (5)	21.6 ± 1.14 (6)	20.8 ± 0.56 (9)
PaO ₂ (mmHg)	91.8 ± 3.53 (20)	81.2 ± 4.34 (25)	101.2* ± 2.30 (35)
PaCO ₂ (mmHg)	44.9 ± 2.35 (23)	51.0* ± 1.77 (26)	42.6 ± 1.31 (35)
PH	7.36 ± 0.016 (23)	7.32 ± 0.012 (26)	7.37 ± 0.012 (35)

Data are Mean ± SE . Numbers in brackets are n. TLC = Total lung capacity (see Methods).

*p < 0.05 vs. controls.

Table 2: BAL Hb, BAL / Plasma Protein, EVLW Ratio, Phospholipids

	CONTROL	POST DECOMPRESSION	
		(0 min)	(60 min)
BAL Hb (ml/100 ml)	0.02 ± 0.014 (11)	0.167 ± 0.097 (11)	0.375*±0.077 (12)
Plasma Protein (g/100 ml)	4.83 ± 0.20 (13)	5.03 ± 0.23 (14)	5.22 ± 0.11 (14)
BAL Protein (g/100 ml) × 10 ⁻³	12.87 ± 1.20 (15)	17.45 ± 2.60 (15)	22.81*±2.22 (16)
BAL Protein/Plasma Protein	2.67 ± 0.26 (13)	3.49 ± 0.53 (14)	4.40*±0.58 (14)
EVLW	4.18 ± 0.05 (18)	4.27 ± 0.08 (22)	4.53*±0.13 (24)
Phosphotidylcholine (mg/gm lung)			
Tissue	3094 ± 551 (7)	4218 ± 605 (12)	4478 ± 747 (12)
BAL	750 ± 101 (11)	668 ± 85 (10)	745 ± 104 (11)
Lysophosphatidylcholine (mg/gm lung)			
Tissue	364 ± 36 (7)	408 ± 36 (12)	356 ± 18 (11)
BAL	2.0 ± 0.4 (10)	4.2* ± 0.8 (10)	7.4*± 1.3 (9)

Data are mean ± SE. Numbers in brackets are n. BAL = bronchoalveolar lavage.

EVLW = extravascular lung water ratio.

* p < 0.05 vs. controls.

TABLE 3. Lung edema, compliance and blood gas data

	CONTROL	TS	VAE	TS-VAE
EVLW	4.18±0.21	3.80±0.41	6.02±0.68*§	4.78±0.73*
Compliance	2.20±0.22	2.10±0.21	2.00±0.08	1.90±0.17
PaO ₂ (mmHg)	89.90±5.18	91.00±8.83	77.20±7.78	75.70±16.86
PaCO ₂ (mmHg)	44.90±2.35	50.30±3.75	47.20±2.33	47.50±5.80
pH	7.35±0.02	7.25±0.02	7.24±0.04	7.27±0.03

Data are represented as mean ± S.D.

*p<0.05 compared with control

p<0.05 compared with TS-VAE

EVLW = extravascular lung water ratio

TABLE 4: Cell counts and protein data

	CONTROL	TS	VAE	TS-VAE
<u>Total WBC</u>				
(cells/mm ³)				
Arterial	7920±386	7831±838	7975±1448	6066±1051
Pulmonary	7970±427	8903±1074	13139±1242*	10457±1840
BAL	674±53	371±61	638±141	880±185
Pleural	54462±5050	60133±9019	20539±3005*	46169±10354
<u>Neutrophils</u>				
(percentage of total WBC)				
Arterial	4.90±1.34	29.60±6.34	70.10±2.99*	68.10±6.28*
Pulmonary	1.27±0.96	24.10±5.17	55.10±4.38*	52.95±31*
BAL	0.68±0.19	2.60±1.66	3.20±1.52	2.30±0.75
Pleural	1.63±0.24	4.60±0.54*	11.40±0.32*	10.60±1.09*
<u>Protein</u>				
(mg/dl)				
Plasma	48.30±2.09	51.92±1.66	50.45±2.33	49.15±2.85
BAL	7.08±0.60	55.00±0.50	20.06±4.92	14.91±8.72
Pleural	18.64±1.14	16.25±1.27	27.68±0.97*	13.77±2.81

WBC = white blood cells

Data are represented as mean ± S.D.

* p<0.05 compared with control

FIGURE LEGENDS

FIGURE 1:

Top; White blood cell count; percentage of neutrophils in three groups. Significant increase in percentages were observed in the bronchoalveolar lavage (BAL) and pleural fluids, 60 min. post decompression.

Bottom; White blood cell counts. Significant increases were observed in the bronchoalveolar lavage (BAL) at 0 min. and 60 min. post decompression and in pulmonary blood 60 min post decompression. Pleural WBC counts were decreased 0 min, returning to control values 60 min post decompression.

FIGURE 2:

Mean arterial blood pressure (MAP) and systemic vascular resistance (SVR) changes with decompression. MAP increased at depth while SVR increased immediately upon surface and 60 min. post decompression.

FIGURE 3:

Cardiac output (CO) decreased at surface and 60 min. post decompression while right ventricular thickening fraction (TF_{RV}) showed parallel responses.

FIGURE 4:

Systemic vascular resistance (SVR) and cardiac output (CO) are plotted as percent change from baseline over time for the TS-VAE and VAE groups. Venous air infusion started at Time = 0 and continued until Time = 3 hrs. TS-VAE SVR values were significantly elevated from the onset of tail-suspension and throughout the air infusion. SVR was also elevated in the VAE group during the air infusion and for 2 hrs. recovery. Cardiac output was decreased significantly from baseline during the air infusion in both groups, and significantly different from each other at 180 min. infusion.

FIGURE 5:

Heart rate (HR) and mean arterial pressure (MAP) are plotted as a function of time. Venous air infusion started at Time = 0 and continued until Time = 3 hrs. MAP values were not significantly changed. HR decreased significantly in both groups during the air infusion.

Figure 1

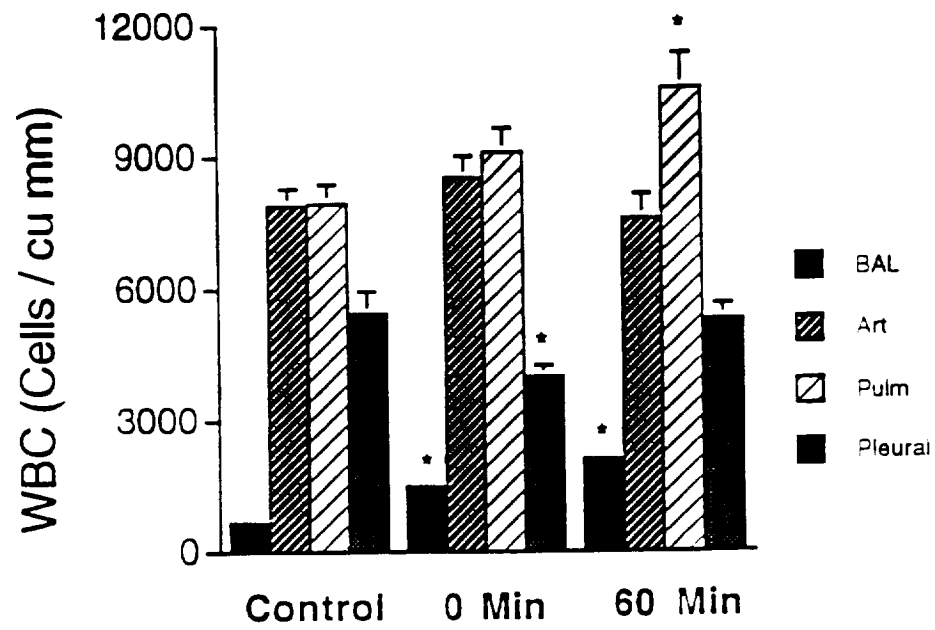
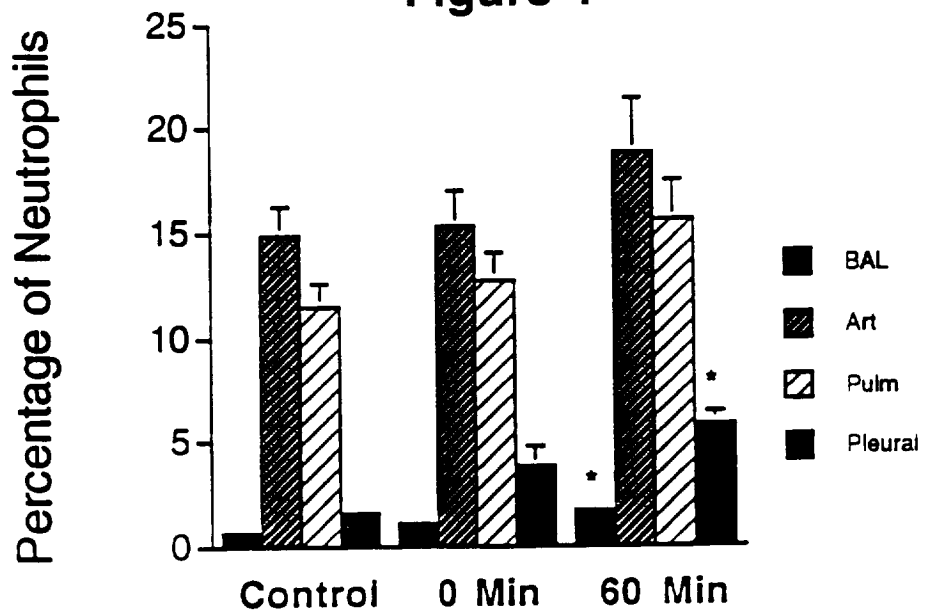


Figure 2

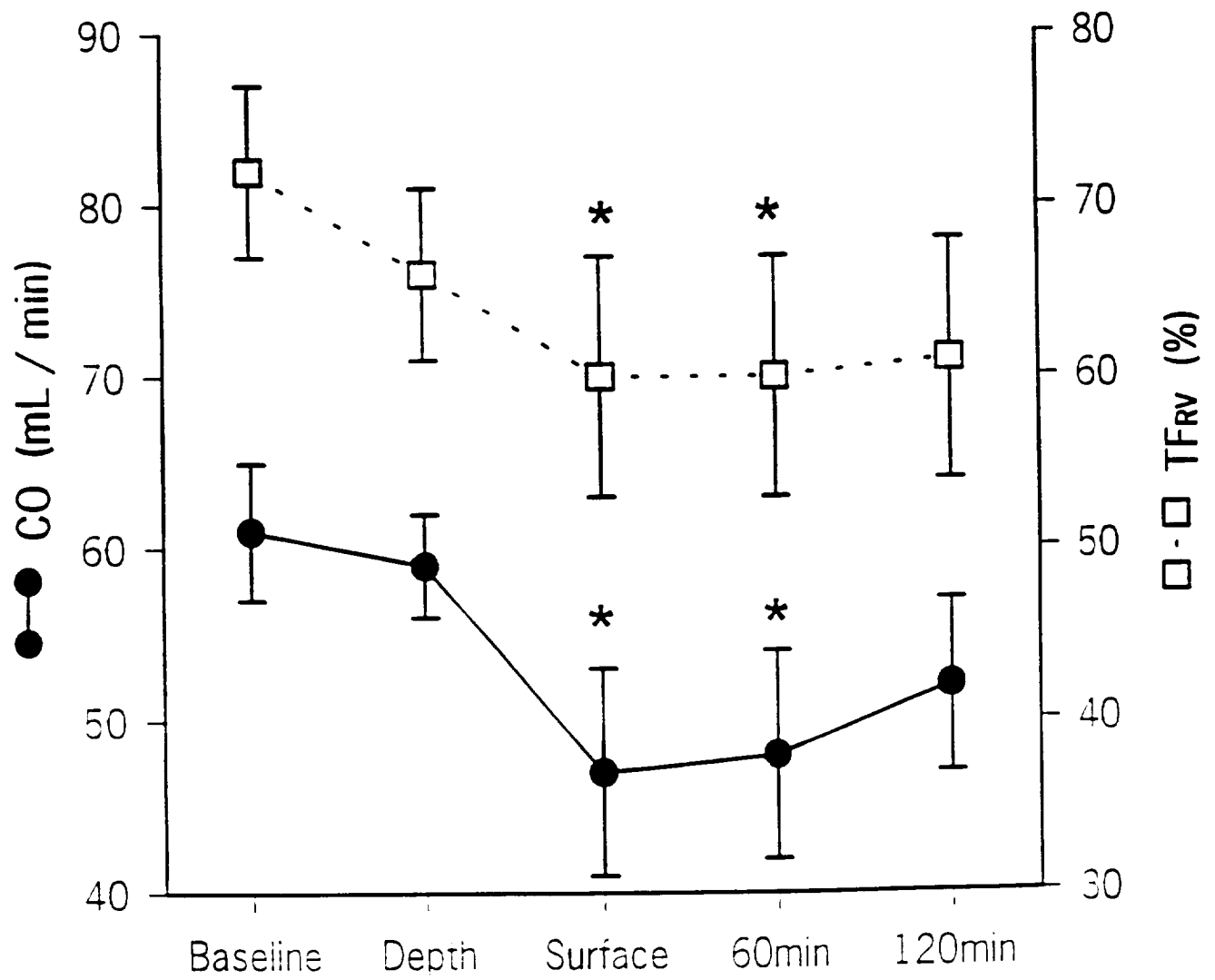


Figure 3

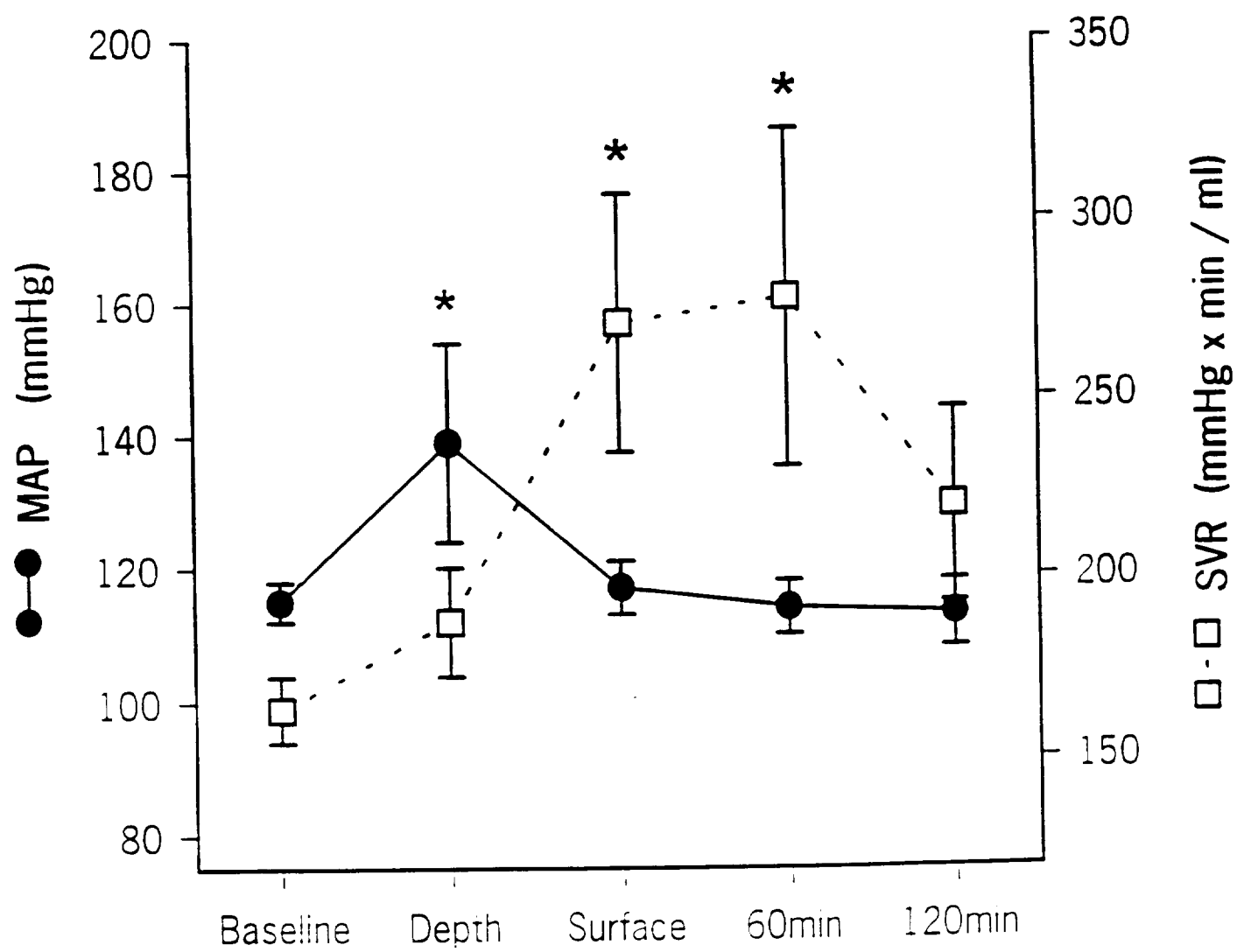


Figure 4

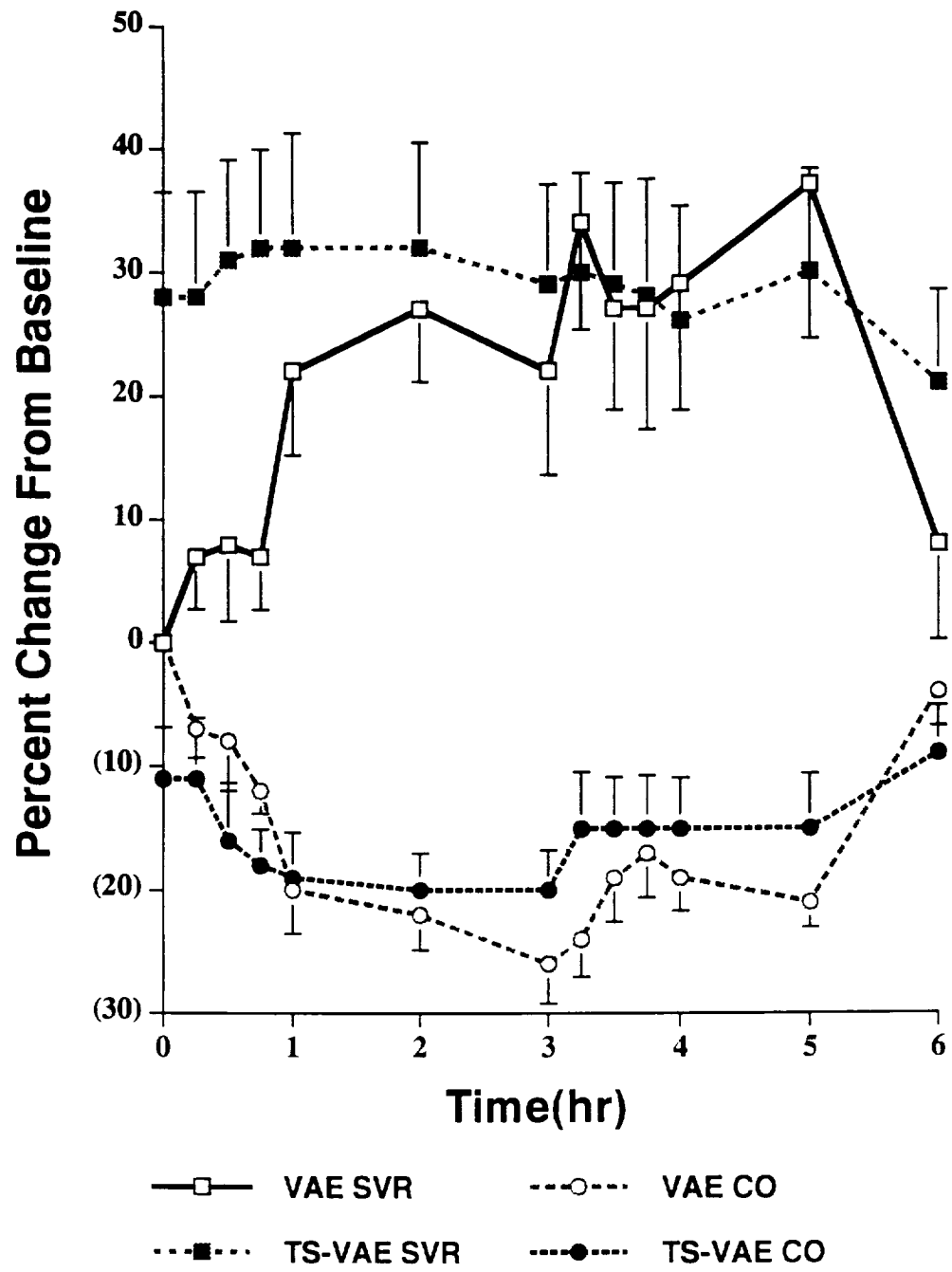


Figure 5

